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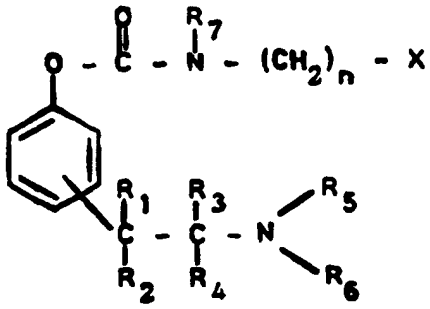
(57) Abstract

Phenylcarbamate derivatives suitable to the use as anticholinesterase substances having general formula (I); wherein the meaning of R_1-R_7 and X substituents together with n will be defined in the text.



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PHENYLCARBAMATE DERIVATIVES SUITABLE TO THE USE AS ANTICHOLINESTERASE SUBSTANCES

PRIOR ART

Various memory disorders and particularly the senile dementia of Alzheimer kind are characterized by a reduction in some cerebral areas of the acetylcholine neurotransmitter levels. In these situations the acetylcholinesterease inhibition, enzyme hydrolizing the acetylcholine, turns out useful for therapeutic aims.

It is known that the physostigmine is a powerful natural inhibitor of the acetylcholinesterase and various clinical studies showed that it gives beneficial results in the treatment of the patients affected by mental pathologies. However the physostigmine has unfavourable pharmacokinetic characteristics and side-effects as to make not very easy its clinical use.

It is also known that eptastigmine or heptylcarbamic ester of the eseroline (EP 0154864), even if it is an acetylcholinesterase inhibitor less powerful "in vitro" than the physostigmine, has with respect to it better pharmacokinetic characteristics and reduced side-effects.

Moreover other drugs, such as for example Tacrine (New Engl. J. Med., 315, 1241 (1986)), Velnacrine (US 4631286), RA_7 (EP 193926), E2020 (EP 296560) are in advanced clinical study for the Alzheimer's disease therapy.

They showed some efficacy but at times together with heavy side-effects too, for example Tacrine and Velnacrine induce high transaminase levels (Eur. Neuropsychopharmacol., 1(3), Abst. S-7-2 (1991)).

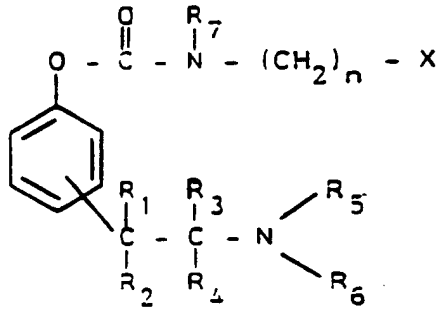
Then the search for new substances having activity inhibiting the

acetylcholinesterase and low toxicity is more and more topical.

SUMMARY

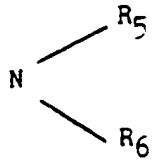
A new class of anticholinesterase compounds which show a higher activity and side-effects lower than the known compounds and moreover have the advantage to be prepared with a simple and economical process has now been found. Moreover some of them carry on a selective activity on the AChE without modifying the BuChE.

Said class of compounds, derivatives of the phenylcarbamate, has the following general formula



wherein R_1, R_2, R_3 and R_4, equal or different, represent: hydrogen, linear or branched (C_1-C_4) alkyl, cycloalkyl (C_3-C_6), arylalkyl, hydroxyl, or R_1 and R_2 together are $-(CH_2)_m-$ wherein m is an integer number from 3 to 6 and form a cycle from 3 to 6 carbon atoms;

R_5 and R_6, equal or different, represent: hydrogen, linear or branched alkyl (C_1-C_6), arylalkyl, acyl or the group:



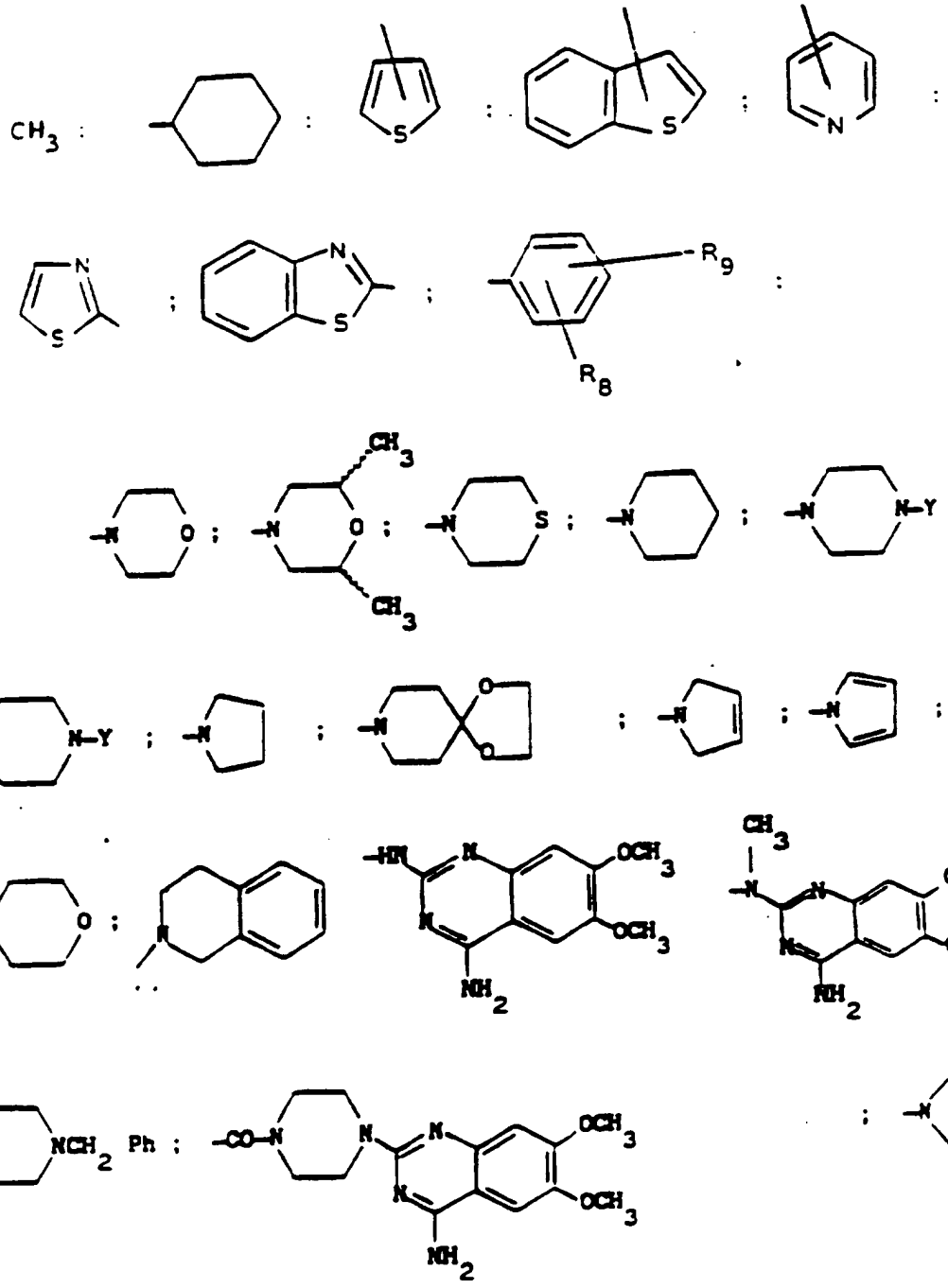
is a radical derivatived from the morpholine, piperidine, tetrahydroquinoline, tetrahydroisoquinoline, alkylpiperazine,

arylpiperazine, arylalkylpiperazine, acylpiperazine, the dialkylaminoalkyl group being in para or meta position with respect to the carbamic group;

R_7 represents hydrogen or a linear or branched (C_1-C_4) alkyl;

n is an integer number from 0 to 20;

X is selected from the radicals

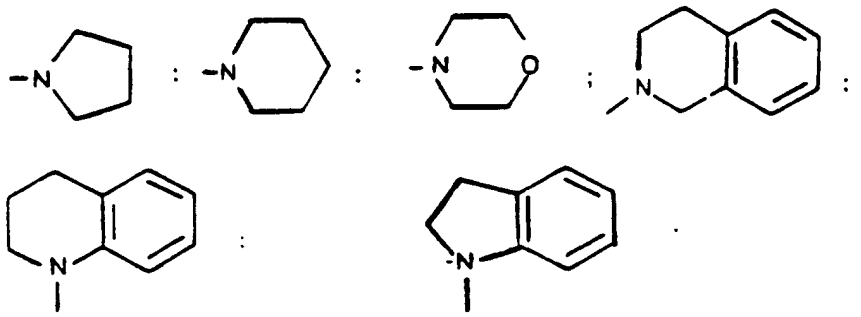


wherein R_8 and R_9, equal or different, represent: linear or branched (C_1-C_4) alkyl, halogen, methoxy, nitro, trifluoromethyl;

Y represents a linear or branched (C_1-C_4) alkyl, acyl, aryl, arylalkyl;

W and Z, equal or different, represent a linear or branched (C_1-C_4) alkyl, arylalkyl, methoxyethyl, methoxypropyl, methoxybenzyl;

or the $-N-(CH_2)_n-X$ (R_7 on N) group is an heterocyclic group such as for example



The compounds having general formula (I) may be salified with pharmacologically acceptable acids selected from the group comprising HCl, HBr, H_2SO_4, H_3PO_4, $HClO_4$, CH_3SO_3H, p-toluenesulfonic acid, citric acid, tartaric acid, maleic acid, salicylic acid, fumaric acid, succinic acid, oxalic acid, and so on.

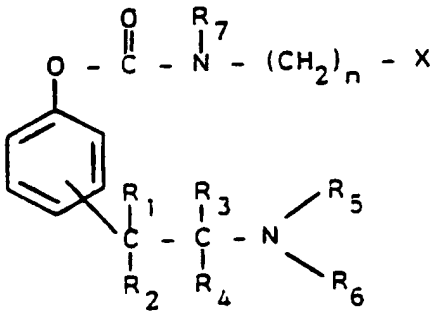
The compounds of the present invention, due to the anticholinesterase activity may be used in human therapy for the treatment of those pathologies which benefit from an acetylcholine increase such as for example the Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

The characteristics and the advantages of the phenylcarbamate derivatives for the use as anticholinesterase substances according to the present invention, and also the process for their preparation, will be mainly pointed out in the course of the following detailed description.

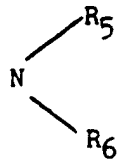
The compounds of the present invention have the following general

formula:



wherein R_1, R_2, R_3 and R_4, equal or different, represent: hydrogen, linear or branched (C_1-C_4) alkyl, cycloalkyl (C_3-C_6), arylalkyl, hydroxyl, or R_1 and R_2 together are $-(CH_2)_m-$ wherein m is an integer number from 2 to 5 and form a cycle from 3 to 6 carbon atoms;

R_5 and R_6, equal or different, represent: hydrogen, linear or branched alkyl (C_1-C_6), arylalkyl, acyl or the group:

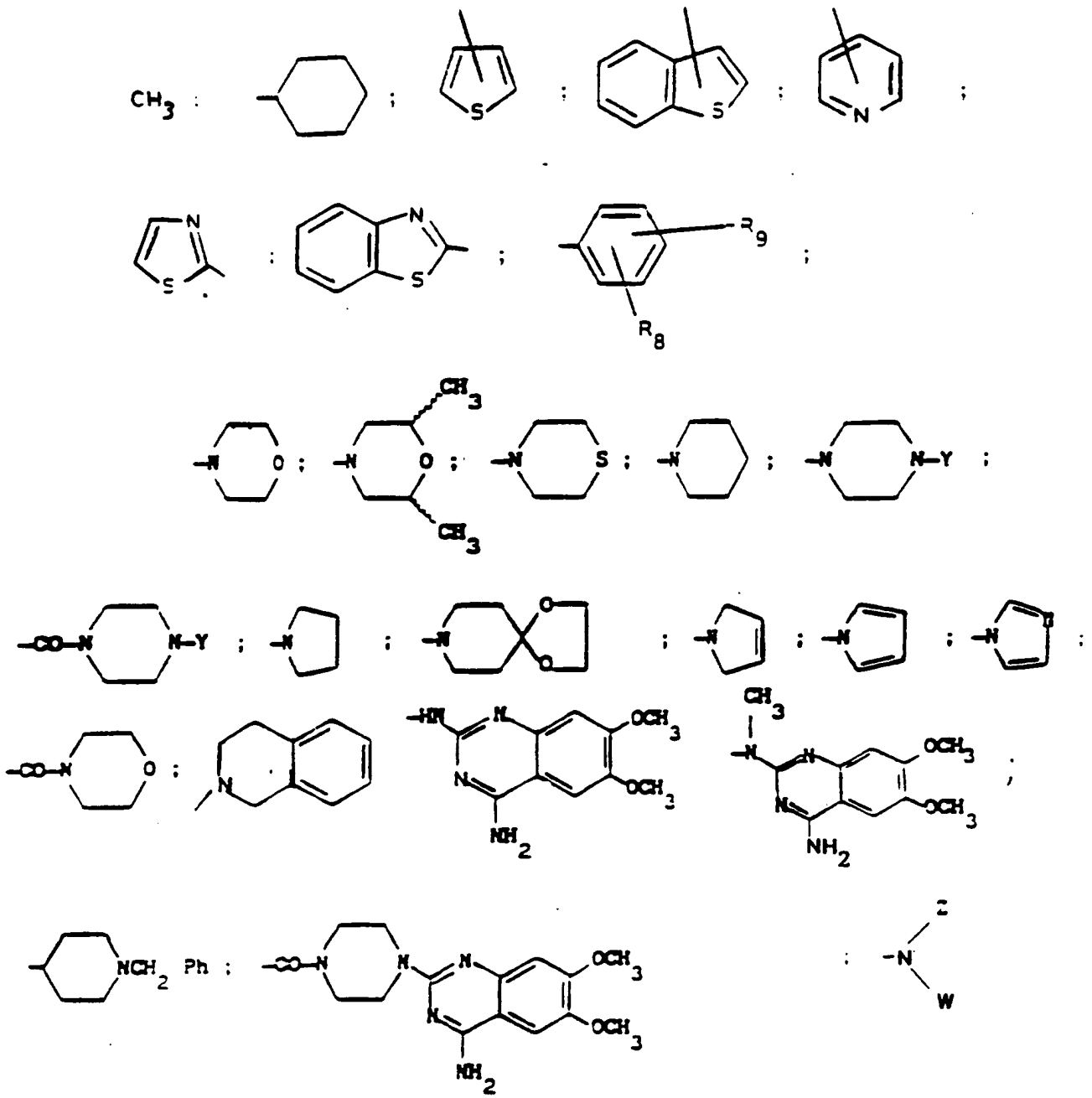


is a radical derivatived from the morpholine, piperidine, tetrahydroquinoline, tetrahydroisoquinoline, alkylpiperazine, arylpiperazine, arylalkylpiperazine, acylpiperazine, the dialkylaminoalkyl group being in para or meta position with respect to the carbamic group;

R_7 represents the hydrogen or a linear or branched (C_1-C_4) alkyl;

n is an integer number from 0 to 20;

X is selected from the radicals

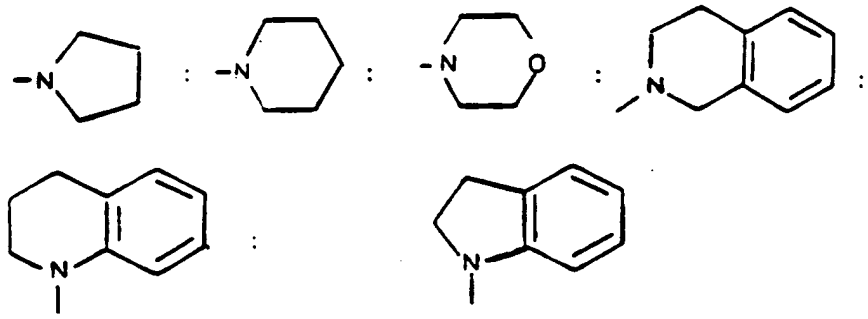


wherein R_8 and R_9, equal or different, represent: linear or branched (C_1-C_4) alkyl, halogen, methoxy, nitro, trifluoromethyl;

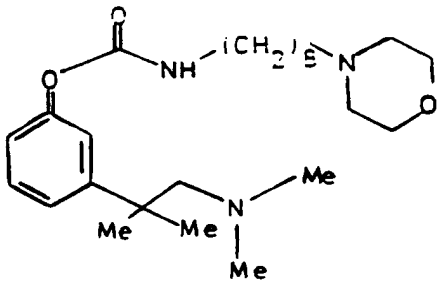
Y represents a linear or branched (C_1-C_4) alkyl, acyl, aryl, arylalkyl;

W and Z, equal or different, represent a linear or branched (C_1-C_4) alkyl, arylalkyl, methoxyethyl, methoxypropyl, methoxybenzyl;

or the $-N-(CH_2)_n-X$ (R_7) group is an heterocyclic group such as for example



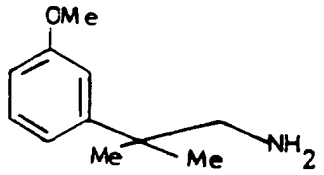
The process for the preparation of the compounds of the invention is described for the compound having formula (II)



(II)

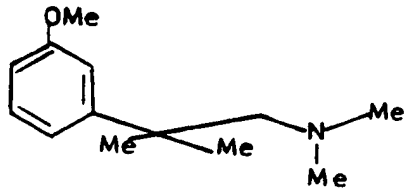
but, as it will be evident from the examples, the same process may be used for the preparation of all the compounds having formula (I) using suitable reacting substances. The compound having formula (II) is prepared through the following steps:

A) The compound having formula (III)



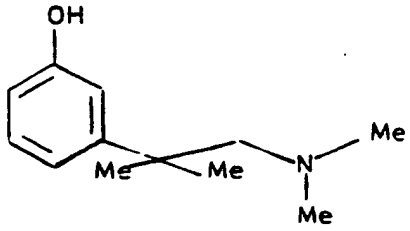
(III)

is made to react with formaldehyde and in reductive amination conditions to obtain the compound (IV)



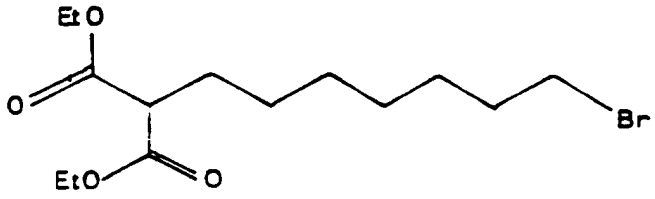
(IV)

B) The compound having formula (IV) is o-demethylated in acidic conditions to obtain the compound having formula (V)



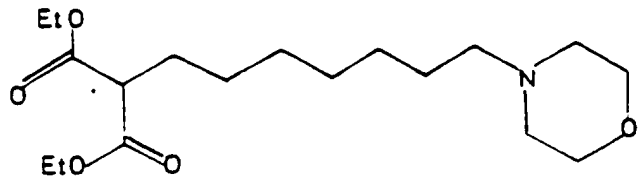
(V)

C) The compound having formula (VI)



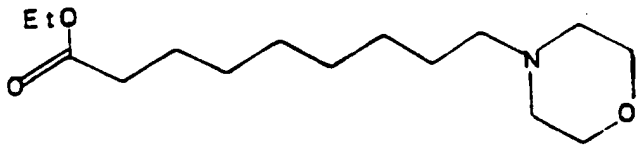
(VI)

is made to react with morpholine to obtain the compound (VII)



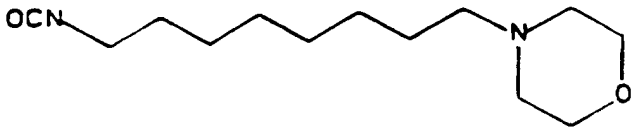
(VII)

D) The compound (VII) is monodecarboxylated to obtain the compound (VIII)



(VIII)

E) The compound (VIII) is submitted to hydrolysis, then transformed in acylazide and by Curtius rearrangement in isocyanate to obtain the compound (IX)



(IX)

F) The compound (V) dissolved in anhydrous toluene, is treated with metallic sodium and subsequently with the compound (IX) to obtain the desired compound (II).

The A) step is carried out preparing a solution in a polar or bipolar aprotic solvent such as methanol, ethanol or acetonitrile of the compound (III) and of formaldehyde in 1:10 molar ratio and adding to this solution a reducing agent as sodium borohydride or sodium cyanoborohydride with 4:1 molar ratio between this compound and the compound (III), cooling the solution so that the temperature is maintained between 2 and 5 °C.

The same reaction may be carried out in formic acid and formaldehyde at a temperature between 50 and 100 °C.

The B) step is carried out treating the compound (IV) with an aqueous solution of HBr at 48 % by weight at a temperature between 25 and 100°C, or using a Lewis acid such as aluminium trichloride, boron trifluoride,

boron tribromide at a temperature between 25 °C and 80 °C in an apolar solvent such as benzene, toluene or chlorobenzene.

In the C) step compound (VI) is made to react with morpholine with molar ratio between (VI) and morpholine between 1:2 and 1:3 in an aprotic bipolar solvent such as for example dimethylformamide, dimethylsulfoxyde, acetone, acetonitrile at room temperature.

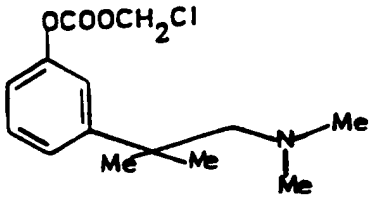
The D) step is carried out making the compound (VII) to react with boric acid with molar ratio between (VII) and boric acid between 1:1 and 1:2 at the acid melting point.The reaction may also be carried out in dimethyl sulfoxide in presence of sodium chloride at a temperature between 100 and 160 °C or heating to fusion the compound (VII) with stearic acid in presence of tetrabutyl phosphonium bromide.

The E) step is carried out treating the compound (VIII) with sodium hydroxide in water to boiling to obtain the sodic salt from it; acetone, tetrabutyl ammonium chlcride and ethyl chloroformate dissolved in acetone at a temperature between -5 and 0 °C are added to it, after cooling, in order to form the mixed anhydride.

The latter by treatment with sodium azide dissolved in water at 0 °C provides the acylazide which heated to boiling is trasformed into isocyanate. The used molar ratios have been the following ones: compound (VIII)/ethyl chloroformate between 1:1 and 1:2 and compound (VIII)/sodium azide between 1:2 and 1:3.

In the F) step the compound (V) dissolved in an apolar solvent such as benzene, xylene, chlorobenzene, toluene is treated with metallic sodium in a molar ratio between (V) and Na between 10:1 and 20:1 and subsequently with the compound (IX) at room temperature with a molar ratio between (V) and (IX) between 1:1 and 1:2.

As an alternative to the described process the compounds having general formula (I) may be prepared by treatment of chloromethylcarbonate having formula (X)



(X)

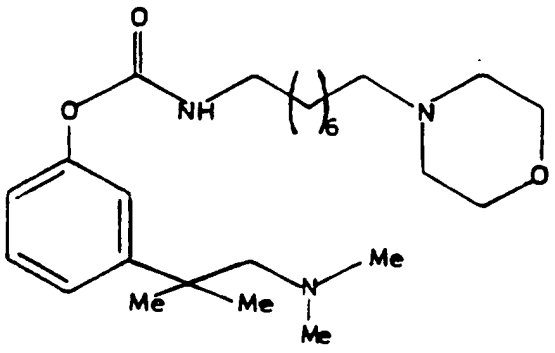
with the suitable amine at room temperature in a bipolar aprotic solvent such as acetonitrile, dimethyl sulfoxide and dimethylformamide with a molar ratio between (X) and amine between 1:1 and 1:2.

For the formulation in pharmaceutical compositions the compounds having general formula (I) may be salified with acids selected from the group comprising HCl, HBr, H_2SO_4, H_3PO_4, $HClO_4$, CH_3SO_3H, p-toluensulfonic acid, citric acid, tartaric acid, maleic acid, salicylic acid, fumaric acid, succinic acid, oxalic acid, and so on.

For explanatory aim of the process for the preparation of the compounds according to the invention the following examples are reported.

EXAMPLE 1

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[8-(4-morpholinyl)octyl]phenylcarbamate (II)



(II)

1A) N,N-2-trimethyl-2-(3-methoxyphenyl)propylamine (IV)

25.3 g (0.403 moles) of sodium cyanoborohydride are added portion by portion and cooling so that the temperature does not exceed 5 °C to a solution of 24.0 g (0.134 moles) of 2-methyl-2-(3-methoxyphenyl)propylamine (III) and 93 ml (1.34 moles) of formaldehyde (40% in water) in 250 ml of acetonitrile. After 15' it is taken to pH=7 with glacial acetic acid and left to room temperature for 1 h. The solvent is evaporated at reduced pressure, the residue is taken back with diethyl ether and an acid-base wash is performed. The organic phase is dehydrated and evaporated at reduced pressure obtaining a yellowish oil constituted by 23.71 g of N,N,2-trimethyl-2-(3-methoxyphenyl)propylamine.

Yield = 85%

Elemental analysis	C	H	N
(theor. %)	73.51	10.21	6.76
(found %)	75.22	10.08	6.85

IR (film, cm^{-1}) : 1040 (ν C-O-C)

^{1}H-NMR($CDCl_3$, ppm): 7.22(1H,t); 6.96(2H,m); 6.71(1H,m); 3.79(3H,s); 2.45(2H,s); 2.07(6H,s); 1.31(6H,s).

1B) 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol (V).

A solution constituted by 10 g (48.2 mmoles) of N,N,2-trimethyl-2-(3-methoxyphenyl)propylamine (IV) in 180 ml of hydrobromic acid at 48% in water is heated to reflux for 4 h. At the end it is concentrated it reduced pressure, it is alkalized to pH=9 and extracted by diethyl ether. The organic phase evaporated at reduced pressure gives a yellowish oil which is crystallized by petroleum ether: isopropyl ether/10:1.

6.84 g of a whitish solid constituted by 3-[(1-dimethylamino-2-)

methyl)prop-2-yl]phenol are obtained.

Yield = 73%

Elemental analysis	C	H	N
(theor. %)	74.57	9.91	7.25
(found %)	74.33	9.72	7.12

^{1}H-NMR($CDCl_3$,ppm): 7.19(1H,m); 6.90(1H,m); 6.75(1H,m); 6.65(1H,m); 2.58(2H,s); 2.09(6H,s); 1.29(6H,s).

1C) 7-(4-morpholinyl)heptyl diethyl malonate (VII).

16 ml (183 mmoles) of morpholine are added to a solution of 28.1 g (83.3 mmoles) of 7-bromo heptyl diethyl malonate (VI) (obtained as described in Bull. Soc. Chim. Fr. 1463 (1957)) in 150 ml of anhydrous acetonitrile and it is left under agitation at room temperature for 20 h.

After such a period the precipitated solid (morpholine hydrobromide) is filtered and washed with little acetonitrile. The solvent is evaporated at reduced pressure and the residue taken back by ethyl acetate and washed with water. The separated organic phase is dehydrated and evaporated at reduced pressure obtaining 28.0 g of 7-(4-morpholinyl)heptyl diethyl malonate.

Yield = 98%

Elemental analysis	C	H	N
(theor. %)	62.95	9.68	4.08
(found %)	62.49	9.57	4.13

IR (film,cm^{-1}) : 1745, 1730 ($\sqrt{}$ C = O).

1D) 9-(4-morpholinyl) ethyl nonanoate (VIII)

27.0 g (78.4 mmoles) of 7-(4-morpholinyl) heptyl diethyl malonate (VII) and 7.3 g (118 mmoles) of boric acid are heated for 5-6 h at the boric

acid melting point (170 °C), distilling the ethanol formed during the reaction.

The reaction mixture is then poured in water and extracted by ethyl acetate. The organic phase is dehydrated and evaporated at reduced pressure obtaining 16.6 g of 9-(4-morpholinyl) ethyl nonanoate.

Yield = 78%

Elemental analysis	C	H	N
(theor. %)	66.38	10.77	5.16
(found %)	65.91	10.81	5.23

IR (film, cm^{-1}) : 1730 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm): 4.05(2H,q); 3.65(4H,t); 2.36(4H,t); 2.30-2.17(4H,m); 1.63-1.23(12H,m); 1.19(3H,t);

1E) 8-(4-morpholinyl)octyl isocyanate (IX).

16.5 g (60.9 mmoles) of 9-(4-morpholinyl)ethyl nonanoate (VIII) are suspended in 50 ml of water, 2.68 g (67.0 mmoles) of sodium hydroxide are added and it is heated to reflux for 30'. At the end the reaction mixture is cooled and extracted by ethyl acetate. 25 ml of acetone, 0.82 g (2.95 mmoles) of tetrabutylammonium chloride are added to the aqueous phase containing the sodic salt and 6.4 ml (78.4 mmoles) of ethyl chloroformate, dissolved in 25 ml of acetone, are dropped, keeping the temperature between -5 °C and 0 °C. After 1 h 8.71 g (134 mmoles) of sodium azide dissolved in 50 ml of water are dropped in the reaction mixture and it is left under agitation at 0 °C for 1 h. After such a period the mixture is extracted several times by toluene, the organic extracts are reunited, dehydrated and heated to 80 °C for 1 h.

At the end it is evaporated at reduced pressure and the residue is distilled at 140-143 °C and 2.5 mmHg.

6.0 g of 8-(4-morpholinyl)octyl isocyanate are obtained.

Yield = 41%

Elemental analysis	C	H	N
(theor. %)	64.96	10.06	11.65
(found %)	64.39	10.19	11.44

IR (film, cm^{-1}) : 2270 (ν N=C=O)

^{1}H-NMR($CDCl_3$, ppm): 3.7(4H,t); 3.25(2H,t); 2.40(4H,t); 2.30(2H,q); 1.70 - 1.20(12H,m).

1F) 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[8-(4-morpholinyl)octyl]-phenylcarbamate (II)

10 mg of metallic sodium are added to a solution of 3.0 g (15.5 moles) of 3-[(dimethylamino-2-methyl)prop-2-yl]phenol (V) in 120 ml of anhydrous toluene at room temperature and in inert atmosphere; after 5' a solution of 4.1 g (17.1 moles) of 8-(4-morpholinyl)octyl isocyanate (IX) in 70 ml of anhydrous toluene is slowly dropped. After 1.5 h the sodium in excess is removed and it is evaporated at reduced pressure.

6.51 g of 3-[(1-dimethylamino)2-methyl)prop-2-yl]-N-8-(4-morpholinyl) octyl]-phenylcarbamate (II) yellowish oil-shaped are obtained.

Yield = 97%

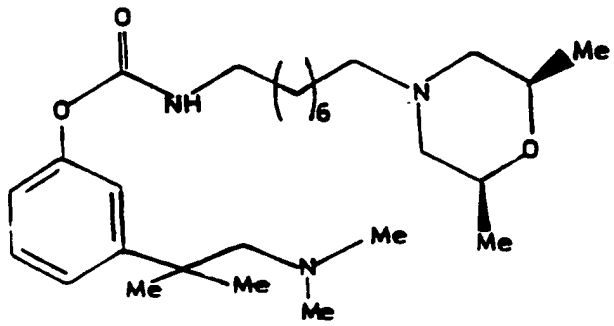
Elemental analysis	C	H	N
(theor. %)	69.25	10.00	9.69
(found %)	68.88	10.08	9.75

IR (film, cm^{-1}) : 3350 (ν N-H); 1740, 1720 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm):7.32-7.15(2H,m);7.12(1H,t);6.94(1H,dt) 5.03(1H,t); 3.72(4H,t); 3.25(2H,q); 2.44(6H,m); 2.31(2H,m); 2.07(6H,m); 1.31(18H,s).

EXAMPLE 2

Synthesis of 3-[(1-dimethylamino-2-methyl)-prop-2-yl]-N-8-[[4-(cis2,6-dimethyl)morpholinyl]octyl]-phenylcarbamate.



Preparation of 7-[4-(cis 2,6-dimethyl)morpholinyl]heptyl diethyl malonate

Acting as described in the Example 1 point 1C) but using as amine the cis 2,6-dimethylmorpholine one obtains the 7-[4-(cis 2,6-dimethyl)morpholinyl] heptyl diethyl malonate.

Yield = 84%

Elemental analysis	C	H	N
(theor. %)	64.66	10.04	3.77
(found %)	64.22	10.21	3.85

IR (film,cm^{-1}) : 1750, 1730 (ν C=O)

Preparation of 9-[4-(cis 2,6-dimethyl)morpholinyl] ethyl nonanoate.

Using 7-[4-(cis 2,6-dimethyl)morpholinyl]heptyl diethyl malonate and acting as described in the Example 1 point 1D) one obtains 9-[4-(cis 2,6-dimethyl) morpholinyl] ethyl nonanoate.

Yield = 81%

Elemental analysis	C	H	N
(theor. %)	68.18	11.11	4.68
(found %)	67.97	11.31	4.74

IR (film,cm^{-1}) : 1730 (ν C=O).

Preparation of 8-[4-(cis 2,6-dimethyl)morpholinyl] octyl isocyanate.

Using 9-[4-(cis 2,6-dimethyl)morpholinyl]ethyl nonanoate and acting as described in the example 1 point 1E) one obtains 8-[4-(cis 2,6-dimethyl)morpholinyl] octyl isocyanate.

Yield = 50%

Elemental analysis	C	H	N
(theor. %)	67.12	10.50	10.44
(found %)	67.61	10.69	10.55

IR (film,cm^{-1}) : 2260 (ν N=C=O)

^{1}H-NMR($CDCl_3$,ppm): 3.35(2H,m); 3.15(2H,t); 2.38(2H,dt); 2.25(2H,dd); 1.70(2H,dd);1.60-1.20(12H,m); 1.10(6H,d).

Preparation of 3-[(1-dimethylamino-2-methyl)-prop-2-yl] -N-8 [4- (cis 2,6-dimethyl) morpholinyl] octyl-phenyl carbamate.

3.80 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[8-[4-(cis 2,6-dimethyl)morpholinyl] octyl]-phenylcarbamate are obtained from 2.09 g (10.8 mmoles) of 3-[(1-dimethylamino-2-methyl)-prop-2-yl]phenol and 2.90 g (10.8 mmoles) of 8-[4-(cis 2,6-dimethyl)morpholinyl] octyl isocyanate using the method described in the Example 1 point 1F).

Yield = 76%

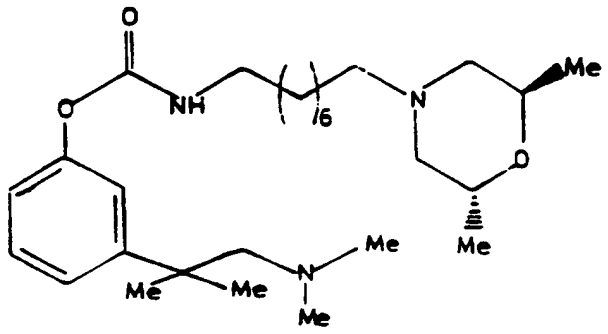
Elemental analysis	C	H	N
(theor. %)	70.24	10.26	9.10
(found %)	70.57	10.03	8.98

IR (film,cm^{-1}) : 3320 (ν N-H); 1740, 1715 (ν C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.27(1H,t); 7.20(1H,dt); 7.11(1H,d); 6.94(1H,dt); 5.00(1H,t); 3.68(2H,m); 3.25(2H,q); 2.74(2H,dt); 2.43(2H,s); 2.28(2H,dd); 2.10(6H,s); 1.70(2H,dd); 1.60-1.40(12H,m); 1.35(6H,s); 1.15(6H,d).

EXAMPLE 3

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[8-[4-(trans 2,6-dimethyl) morpholinyl] octyl]-phenylcarbamate.



Preparation of 8-[4-(trans 2,6-dimethyl)morpholinyl] octyl isocyanate.

Acting as described in the Example 1 points 1C), 1D), 1E) but using trans 2,6-dimethylmorpholine (obtained as described in the Patent DE 2656747) one obtains 8-[4-(trans 2,6-dimethyl)morpholinyl]octyl isocyanate.

Elemental analysis	C	H	N
(theor. %)	67.12	10.50	10.44
(found %)	66.85	10.39	10.27

Preparation of 3-[(1-dimethylamino-2-methyl)-prop-2-yl]-N-[8-[4-(trans 2,6-dimethyl)morpholinyl]octyl]-phenylcarbamate

1.67 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[8-[4-(trans 2,6-dimethyl)morpholinyl]octyl]-phenylcarbamate are obtained from 1.0 g (5.17 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol and 1.4 g (5.17 mmoles) of 8-[4-(trans 2,6-dimethyl) morpholinyl]octyl isocyanate using the method described in the Example 1 point 1F).

Yield = 70%

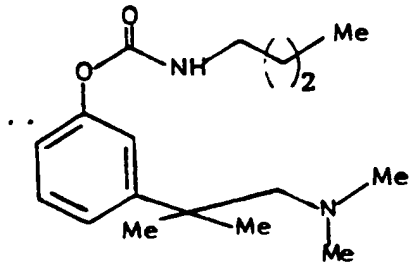
Elemental analysis	C	H	N
(theor. %)	70.24	10.26	9.10
(found %)	70.63	10.11	9.32

IR (film,cm^{-1}) : 3320 (ν N-H); 1740, 1715 (ν C=0)

^{1}H-NMR($CDCl_3$,ppm): 7.28(1H,t); 7.19(1H,dt); 7.10(1H,d); 6.90(1H,dt); 5.35(1H,t); 3.60(2H,m); 3.15(2H,q); 2.70(2H,m); 2.40(2H,s); 2.20(2H,m); 2.00(6H,s); 1.60(2H,t); 1.20(18H,m); 1.05(6H,d).

EXAMPLE 4

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-butylphenyl carbamate.



0.48 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-butylphenyl carbamate are obtained from 0.4 g (2.0 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol and 0.2 g (2.0 mmoles) of butyl isocyanate using the method described in the Example 1 point 1F).

Yield = 80%

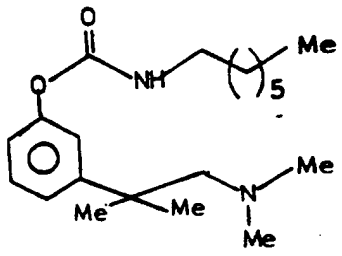
Elemental analysis	C	H	N
(theor. %)	69.82	9.65	9.58
(found %)	69.50	9.75	9.30

IR (film,cm^{-1}) : 3330 (ν N-H); 1740, 1720 (ν C=0)

^{1}H-NMR($CDCl_3$,ppm): 7.35-6.80(4H,m); 4.92(1H,s all); 3.21(2H,q); 2.40(2H,s); 2.02(6H,s); 1.42(4H,m); 1.27(6H,s); 0.87(3H,t).

EXAMPLE 5

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-heptyl-phenyl carbamate.



0.21 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-heptyl-phenyl carbamate are obtained from 0.16 g (0.83 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol and 0.12 g (0.83 mmoles) of heptyl isocyanate using the method described in the Example 1 point 1F).

Yield = 75%

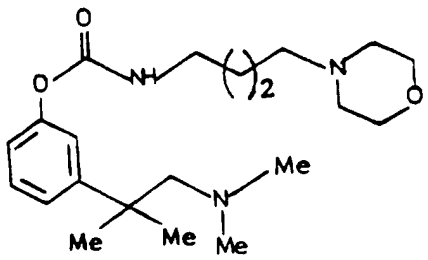
Elemental analysis	C	H	N
(theor. %)	71.81	10.24	8.37
(found %)	71.49	9.95	8.00

IR (film, cm^{-1}) : 3320 ($\bar{\nu}$ N-H); 1740, 1720 ($\bar{\nu}$ C=O)

^{1}H-NMR($CDCl_3$, ppm): 7.35-6.80(4H,m); 4.92(1H,s all); 3.21(2H,q); 2.40(2H,s); 2.07(6H,s); 1.60-1.10(10H,m); 1.27(6H,s); 0.80(3H,t).

EXAMPLE 6

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[4-(4-morpholinyl)butyl]-phenyl carbamate.



Preparation of 4-(4-morpholinyl)butyl isocyanate.

A solution constituted by 3.16 g (0.02 moles) of 4-(4-morpholinyl)butyl amine and 16.7 ml (0.12 moles) of triethylamine in 60 ml of toluene is dropped in 15.5 ml (0.03 moles) of phosgene (20% in toluene) kept at 0 °C and in inert atmosphere for about 20'. It is left to react at 0 °C for 3 h and then the solvent is removed at reduced pressure. The residue taken beck by dioxane gives a white solid (triethyl amine hydrocloride) which is filtered. The dioxane is evaporated at reduced pressure and the obtained residue distilled between 200 and 240 °C at 0.5 mmHg. 2.4 g of 4-(4-morpholinyl)butyl isocyanate are recovered.

Yield = 65%

Elemental analysis	C	H	N
(theor. %)	58.67	8.75	15.21
(found %)	58.42	8.50	14.98

IR (film, cm^{-1}) : 2280 (ν N=C=O).

Preparation of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[4-(4-morpholinyl)butyl]-phenyl carbamate.

0.73 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[4-(4-morpholinyl)butyl]-phenyl carbamate are obtained from 0.45 g (1.67 mmoles) of the 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol and 0.43 g (1.67 mmoles) of 4-(4-morpholinyl)butyl isocyanate using the method described in the Example 1 point 1F).

Yield = 83%

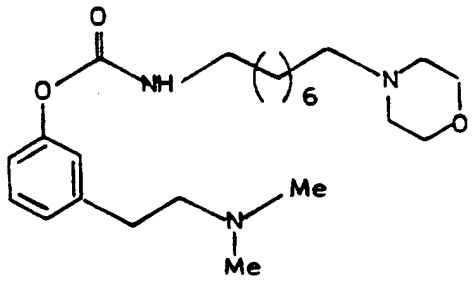
Elemental analysis	C	H	N
(theor. %)	66.81	9.34	11.13
(found %)	66.55	9.37	10.85

IR (film, cm^{-1}) : 3340 (ν N-H); 1735, 1725 (ν C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.36-6.85(4H,m); 5.04(1H,s all); 3.71(4H,m); 3.25(2H,q); 2.49-2.20(8H,m); 2.15(6H,s); 1.60(4H,m); 1.35(6H,s).

EXAMPLE 7

Synthesis of 3-[2-(dimethylamino)ethyl]-N-[8-(morpholinyl)octyl]-phenyl carbamate.



1 g of 3-[2-(dimethylamino)ethyl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate is obtained from 0.50 g (3.03 mmoles) of 3-[2-(dimethylamino)ethyl]phenol and 0.73 g (3.03 mmoles) of 8-(4-morpholinyl)octyl isocyanate using the method described in the Example 1 point 1F).

Yield = 80%

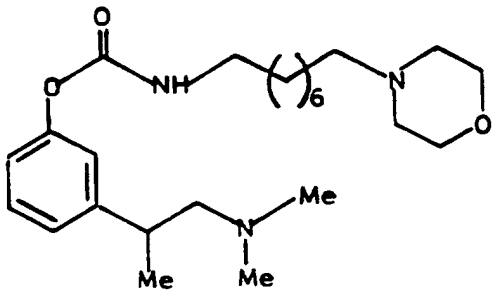
Elemental analysis	C	H	N
(theor. %)	68.11	9.69	10.36
(found %)	67.94	9.84	10.08

IR (film,cm^{-1}) : 3360 (ν N-H); 1740, 1720 (ν C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.30(1H,t); 7.00(3H,m); 5.20(1H,t); 3.70(4H,t); 3.25(2H,q); 2.80-2.50(4H,m); 2.45(4H,t); 2.35(2H,m); 2.30(6H,s); 1.30(12H,m).

EXAMPLE 8

Synthesis of the 3-[(1-dimethylamino)prop-2-yl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate.



Preparation of 3-[(1-dimethylamino)prop-2-yl]phenol.

Using N,N-dimethyl-2-(3-methoxyphenyl)propylamine and acting as described in the Example 1 point 1B) 3-[(1-dimethylamino)prop-2-yl]phenol is obtained.

Yield = 77%

Elemental analysis	C	H	N
(theor. %)	73.70	9.56	7.81
(found %)	73.37	9.62	7.74

IR (film, cm^{-1}) : 3300 (ν O-H)

^{1}H-NMR($CDCl_3$, ppm): 7.58(1H,m); 7.00(1H,t); 6.60(1H,m); 6.40(2H,m); 3.28(2H,m); 2.35(1H,q); 2.20(6H,s); 1.10(3H,d).

Preparation of 3-[(1-dimethylamino)prop-2-yl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate.

0.79 g of 3-[(1-dimethylamino)prop-2-yl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate are obtained from 0.45 g (2.5 mmoles) of 3-[(1-dimethylamino)prop-2-yl]phenol and 0.62 g (2.5 mmoles) of 8-(4-morpholinyl)octyl isocyanate using the method described in the Example 1 point 1F).

Yield = 75%

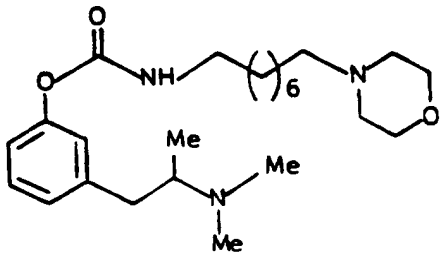
Elemental analysis	C	H	N
(theor. %)	68.70	9.85	10.01
(found %)	68.28	9.96	10.11

IR (film, cm^{-1}) : 3350 (ν N-H); 1730, 1710 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm): 7.10 (1H,t); 6.95(3H,m); 5.25(1H,t); 3.60(4H,t); 3.18(2H,q); 2.80(1H,q); 2.38(4H,t); 2.25(4H,m); 2.18(6H,s); 1.40-1.30(12H,m); 1.20(3H,d).

EXAMPLE 9

Synthesis of 3-[2-(dimethylamino)propyl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate.



Preparation of 3-[2-(dimethylamino)propyl]phenol.

Using N,N,2-trimethyl-(3-methoxyphenyl)ethylamine and acting as described in the Example 1 point 1B) 3-[2-(dimethylamino)propyl]phenol is obtained.

Yield = 76%

Elemental analysis	C	H	N
(theor. %)	73.70	9.56	7.81
(found %)	73.81	9.45	7.70

IR (film, cm^{-1}) : 3450 (ν O-H)

^{1}H-NMR($CDCl_3$, ppm): 7.40 (1H,m); 7.10(1H,t); 6.90(3H,m); 2.80(2H,m);

2.30(1H,q); 2.20(6H,s); 0.80(3H,d).

Preparation of 3-[2-(dimethylamino)propyl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate.

1.02 g of 3-[2-(dimethylamino)propyl]-N-[8-(4-morpholinyl)octyl]-phenyl carbamate are obtained from 0.51 g (2.8 mmoles) of 3-[2-(dimethylamino)propyl] phenol and 0.68 g (2.8 mmoles) of 8-(mopholinyl) octyl isocyanate using the method described in the Example 1 point 1F).

Yield = 86%

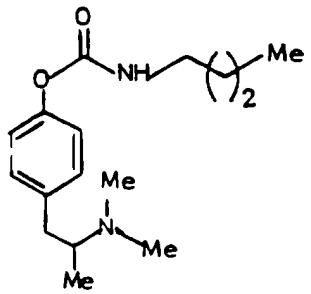
Elemental analysis	C	H	N
(theor. %)	68.70	9.85	10.01
(found %)	68.38	9.93	10.18

IR (film,cm^{-1}) : 3320 ($\bar{\nu}$ N-H); 1740 ($\bar{\nu}$ C=0)

^{1}H-NMR($CDCl_3$,ppm): 7.10 (1H,t); 6.90(3H,m); 5.20(1H,t); 3.65(4H,t); 3.18(2H,q); 2.90(2H,dd); 2.70(1H,m); 2.37(4H,t); 2.28(2H,m); 2.25(6H,s); 1.50-1.30(12H,m); 0.80(3H,d).

EXAMPLE 10

Synthesis of 4-[2-(dimethylamino)propyl]-N-butyl-phenyl carbamate.



0.6 g of 4-[2-(dimethylamino)propyl]-N-butyl-phenyl carbamate are obtained from 0.50 g (2.79 mmoles) of 4-[2-(dimethylamino)propyl]phenol

and 0.28 g (2.79 mmoles) of the butyl isocyanate using the method described in the Example 1 point 1F).

Yield = 77%

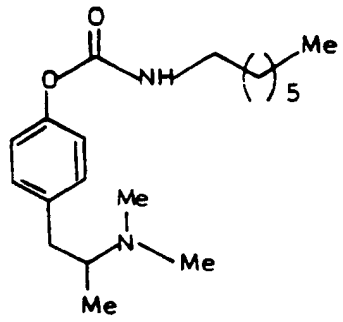
Elemental analysis	C	H	N
(theor. %)	69.03	9.41	10.06
(found %)	68.77	9.50	10.20

IR (film, cm^{-1}) : 3320 (ν N-H); 1730 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm): 7.12-6.88(4H,m); 4.93(1H,t); 3.22(2H,q); 3.00-2.60(3H,m); 2.25(6H,s); 1.66-1.20(4H,m); 0.95-0.80(6H,m).

EXAMPLE 11

Synthesis of 4-[2-(dimethylamino)propyl]-N-heptyl-phenyl carbamate.



0.38 g of 4-[2-(dimethylamino)propyl]-N-heptyl-phenyl carbamate are obtained from 0.30 g (1.67 mmoles) of 4-[2-(dimethylamino)propyl]phenol and 0.24 g (1.67 mmoles) of heptyl isocyanate using the method described in the Example 1 point 1F).

Yield = 71%

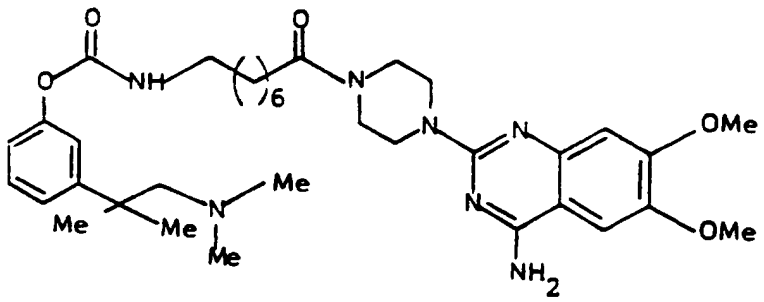
Elemental analysis	C	H	N
(theor. %)	71.43	9.78	8.77
(found %)	71.09	9.55	8.67

IR (film,cm^{-1}) : 3320 (ν N-H); 1730 (ν C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.15-6.90(4H,m); 4.95(1H,t); 3.20(2H,q); 2.85-2.60(3H,m); 2.32(6H,s); 1.50-1.15(10H,m); 0.95-0.82(6H,m).

EXAMPLE 12

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[4-(4-amino-6,7-dimethoxy)quinazolin-2-yl]piperazinyl]-8-octanoyl]-phenyl carbamate.



12A) 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-bromooctanoyl) piperazine.

2.1 ml (0.015 moles) of anhydrous triethylamine and subsequently 1.4 ml (0.015 moles) of ethylchloroformate are added at 0 °C and under inert atmosphere to a solution constituted by 5.0 g (0.022 moles) of 8-bromooctanoic acid in 50 ml of anhydrous dimethylformamide. It is taken to room temperature and after 1.5 h 3.6 g (0.012 moles) of 1-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]piperazine (obtained as described in J. Med. Chem. 20, 146 (1977)) dissolved in 80 ml of anhydrous dimethylformamide are added.

After 4 h the solvent is evaporated at reduced pressure and the obtained residue is washed in water and filtered.

5.50 g of 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-bromooctanoyl)piperazine are isolated.

Yield = 93%

Elemental analysis	C	H	N
(theor. %)	53.44	6.52	14.16
(found %)	52.88	6.74	13.84

IR (nujol, cm^{-1}): 3380, 3340, 3220 (ν N-H); 1650 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm): 7.05(1H,s); 6.90(1H,s); 5.50(2H,s broad); 3.92(3H,s); 3.90(3H,s); 3.85(2H,m); 3.78(2H,m); 3.65(2H,m); 3.50(2H,m); 3.35(2H,t); 2.32(2H,t); 1.80(2H,m); 1.58(2H,m); 1.30(6H,m).

12B) 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-phthalimido octanoyl)piperazine.

26.73 g (0.054 moles) of 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-bromooctanoyl)piperazine, 10.01 g (0.054 moles) of potassium phthalimide and 0.1 g of sodium iodide (catalytic quantity) are suspended in 500 ml of anhydrous dimethylformamide and heated to 80 °C for 15 h. At the end the solvent is evaporated at reduced pressure, 300 ml of water are added and it is extracted by chloroform. The organic phase is dehydrated, evaporated at reduced pressure and chromatographed on silica gel using petroleum ether: chloroform: methanol: triethylamine / 8:5:1:1 as eluant. The end fractions are gathered and dried.

23.12 g of 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-phthalimido octanoyl)piperazine as a yellowish solid are obtained.

Yield = 76% m.p. = 172.5 - 174 °C

Elemental analysis	C	H	N
(theor. %)	64.27	6.47	14.99
(found %)	63.88	6.74	15.32

IR (nujol, cm^{-1}): 3430, 3330, 3200 (ν N-H); 1760, 1700, 1620 (ν C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.78(2H,m); 7.65(2H,m); 6.85(1H,s); 6.75(1H,s); 5.16(2H,s); 3.92(3H,s); 3.86(3H,s); 3.76(4H,m); 3.61(4H,m); 3.45(2H,m); 2.30(2H,m); 1.60(4H,m); 1.30(6H,m).

12C) 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-aminooctanoyl) piperazine.

An etherogeneous solution constituted by 1.92 g (3.42 mmoles) of 4-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]-1-(8-phthalimido octanoyl)piperazine and 0.5 ml (8.24 mmoles) of hydrazine monohydrate (80% in water) in 40 ml of ethanol is heated to reflux for 3 h. Then the solution is concentrated to about half the volume and added with 2 ml of hydrochloric acid at 36%. The obtained precipitate is filtered and washed with ethanol; the bitterns are evaporated at reduced pressure and the residue is taken back with 10 ml of water. It is taken to pH=10 by sodium hydroxide and extracted by chloroform.

The separated organic phase is dehydrated and evaporated obtaining 1.40 g of a whitish solid constituted by 4-[(4-amino-6,7-dimethoxy) quinazolin-2-yl]-1-(8-aminooctanoyl) piperazine.

Yield = 96%

Elemental analysis	C	H	N
(theor. %)	61.37	7.96	19.52
(found %)	60.88	8.47	18.94

IR (nujol,cm^{-1}): 3400, 3340, 3220 (ν N-H);

^{1}H-NMR($CDCl_3$,ppm): 6.85(1H,s); 6.75(1H,s); 5.20(2H,s); 3.91(3H,s); 3.85(3H,s); 3.75(4H,m); 3.65(2H,m); 3.45(2H,m); 2.60(2H,t); 2.30(2H,t); 1.58(2H,m); 1.45-1.25(10H,m).

12D) 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenyl chloromethyl carbonate.

A solution of 0.10 ml (1.13 mmoles) of chloromethyl chloroformate in 10 ml of anhydrous methylene chloride is dropped at a temperature lower than 5 °C to a solution of 0.20 g (1.03 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenol and 0.15 ml (1.08 mmoles) of anhydrous triethylamine in 10 ml of anhydrous methylene chloride and it is left reacting for 2 h at room temperature. At the end it is washed first with a solution of sodium bicarbonate at 10% then with water.

The organic phase is dehydrated and evaporated at reduced pressure obtaining 0.28 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenyl chloromethyl carbonate.

Yield = 95%

Elemental analysis	C	H	N
(theor. %)	58.84	7.05	4.90
(found %)	58.55	7.25	4.76

IR (film,cm^{-1}): 1770 ($\bar{\nu}$ C=O)

^{1}H-NMR($CDCl_3$,ppm): 7.30-7.00(4H,s); 5.75(2H,s); 2.47(2H,s); 2.06(6H,m); 1.29(6H,s).

12E) 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[1-[4-[(amino-6,7 dimethoxy)quinazolin-2-yl]piperazinyl]-8-octanoyl]-phenyl carbamate.

0.45 g (1.05 mmoles) of 4-[(4-amino-6,7 dimethoxy) quinazolin-2-yl]-1-(8-aminooctanoyl) piperazine are added at room temperature to a solution of 0.30 g (1.05 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl] phenyl chloromethyl carbonate in 7 ml of anhydrous dimethylformamide and it is left reacting for 1 h at room temperature. At the end 30 ml of water are added and it is extracted by chloroform. The dehydrated organic phase is evaporated at reduced pressure and the residue is chromatographed using petroleum ether: acetone: triethylamine/12:9:1 as eluant.

0.60 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[1-[4-(4-amino-6,7-dimethoxy)quinazolin-2-yl]piperazinyl]-8-octanoyl]-phenyl carbamate are obtained.

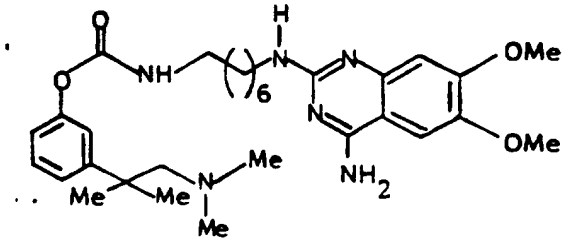
Yield = 88%

Elemental analysis	C	H	N
(theor. %)	64.69	7.91	15.09
(found %)	64.33	7.75	15.15

^{1}H-NMR($CDCl_3$,ppm): 7.21-6.80(6H,m); 5.17(2H,s widened); 5.00(1H,t); 3.99(3H,s); 3.91(3H,s); 3.85(4H,m); 3.70(2H,m); 3.52(2H,m); 3.25(2H,m); 2.48(2H,s); 2.38(2H,t); 2.10(6H,s); 1.70-1.10(16H,m).

EXAMPLE 13

Synthesis of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[N-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]aminoheptyl]-phenyl carbamate.



Preparation of N-[(4-amino-6,7-dimethoxy)quinazolin-2-yl]heptandiamine.

7.7 g (32 mmoles) of 4-amino-2-chloro-6,7-dimethoxyquinazoline are suspended in 250 ml of anhydrous butanol.

12.6 g (97 mmoles) of 1.7-diaminoheptane are added and the mixture is heated to reflux for 15 h. The solvent is evaporated at reduced pressure and the obtained residue is taken back by chloroform and washed by basic water.

12 g of raw product are obtained which by chromatographic purification (methylene chloride : methanol : ammonium hydroxyde 32% / 8:2:0.2 as eluant) gives 5.7 g of N-[(4-amino-6,7-dimethoxy)quinazolin-2-

yl]heptandiamine.

Yield = 51%

Elemental analysis	C	H	N
(theor. %)	61.23	8.16	21.00
(found %)	61.15	8.24	20.87

IR (nujol, cm^{-1}): 3300, 3110 (ν N-H)

^{1}H-NMR($CDCl_3$, ppm): 7.40(1H,s); 6.95(2H,m); 6.65(1H,s); 6.00(1H,m); 3.80(3H,s); 3.75(3H,s); 3.25(2H,m); 2.47(2H,m); 1.40-1.10(10H,m).

Preparation of 3-[(1-dimethylamino-2-methyl)prop-2-yl] -N- [N- [(4- amino -6,7 -dimethoxy) quinazolin -2-yl] aminoheptyl-phenyl carbamate.

0.54 g of 3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[N-[4-amino-6,7-dimethoxy)quinazolin-2-yl]aminoheptyl-phenyl carbamate are obtained from 0.6 g (2.1 mmoles) of 3-[(1-dimethylamino-2-methyl)prop-2-yl]phenyl chloromethyl carbonate and 0.5 g of N-[(4-amino-6,7-dimethoxy) quinazolin-2-yl]heptandiamine using the method described in the Example 12 point 12E).

Yield = 65%

Elemental analysis	C	H	N
(theor. %)	65.19	8.02	15.21
(found %)	65.07	8.11	15.09

IR (nujol, cm^{-1}): 3280 (ν NHC=O); 3180 (ν N-H); 1720 (ν C=O)

^{1}H-NMR($CDCl_3$, ppm): 7.70-(1H,s); 7.50(2H,m); 7.30-7.10(4H,m); 6.95(1H,m); 6.78(1H,s); 5.50(1H,t); 4.00(3H,s); 3.90(3H,s); 3.40(2H,t); 3.30(2H,t); 2.60(2H,s); 2.15(6H,s); 1.50-1.30(16H,m).

EXAMPLES FROM 14 TO 28

The following compounds have been prepared by processes analogous to those ones previously described:

3-[(1-dimethylamino-2-ethyl)-but-2-yl]-N-[8-(4-morpholinyl)octyl)]-phenyl-carbamate (Example 14);

3-[(1-dimethylamino-2-methyl)-prop-2-yl]-N-[2-(4-morpholinyl)ethyl]-phenyl-carbamate (Example 15);

3-[(1-(N-benzyl-N-methyl)amino-2-methyl)prop-2-yl]-N-[8-(4-morpholinyl)-octyl]-phenylcarbamate (Example 16);

3-[(1-dipropylamino-2-methyl)prop-2-yl]-N-[8-(4-morpholinyl)octyl]-phenyl-carbamate (Example 17);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-[10-(4-morpholinyl)decyl]-phenyl-carbamate (Example 18);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-phenyl phenylcarbamate (Example 19);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-fluoro)phenyl phenyl-carbamate (Example 20);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-methyl)phenyl phenyl-carbamate (Example 21);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-methoxy)phenyl phenyl-carbamate (Example 22);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-chloro)phenyl phenyl-carbamate (Example 23);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-benzyl-phenylcarbamate (Example 24);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-phenyl-N-methyl-phenyl-carbamate (Example 25);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-chloro)-phenyl-N-methyl-phenylcarbamate (Example 26);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-ethyl-N-methyl-phenylcarbamate (Example 27);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-indolinyl-phenylcarbamate (Example 28);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-ethyl-N-phenyl phenylcarbamate (Example 29);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-phenyl-N-propyl phenylcarbamate (Example 30);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(2-methoxy)phenyl-N-methyl phenylcarbamate (Example 31);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-butyl-N-phenyl phenylcarbamate (Example 32);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-methyl-N-(2-methyl)phenyl phenylcarbamate (Example 33);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-cyclohexyl-N-ethyl phenylcarbamate (Example 34);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-methyl-N-(4-methoxy)phenyl phenylcarbamate (Example 35);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-ethyl-N-(4-methoxy)phenyl phenylcarbamate (Example 36);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(4-chloro)phenyl-N-methyl phenylcarbamate (Example 37);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-(3-fluoro)phenyl-N-methyl phenylcarbamate (Example 38);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-methyl-N-(3-trifluoromethyl)

phenyl phenylcarbamate (Example 39);

3-[(1-dimethylamino-2-methyl)prop-2-yl]-N-cyclohexyl-N-methyl phenylcarbamate (Example 40).

PHARMACOLOGICAL EXPERIMENTATION

The compounds prepared as decribed in the above mentioned examples have been studied in a pharmacological experimentation aimed to the determination of the inhibitory activity of the acetylcholinesterase and the butyrylcholinesterase. The method of Ellman et al. (Ellman G.L., Courtney K.D., Andres V., Featherstone R.M.: a New and Rapid Colorimetric Determination of Acetylcholinesterase Activity, Biochem. Pharm. 7,88, 1961) has been used.

The incubation time between enzyme and product used for the determinations has been 10'.

The acetylcholinesterase from human erythrocytes (AChE hRBC), the acetylcholinesterase from Electric Eel (AChE E.eel) and the butyrylcholinesterase from human serum (BuChE hserum) coming from the Sigma Chemical have been used.

The obtained results are reported in the Table 1. In said table the results obtained by eptastigmine, physostigmine and tacrine (9-amino-1,2,3,4-tetrahydroacridine) which are known anticholinesterase substances are reported by comparison.

TABLE 1

Inhibition of the cholinesterase (IC_{50} M)

Compound	AChE E. eel	AChE hRBC	BuChE hserum
Ex. 1	4.7×10^{-7}	1.6×10^{-7}	1.6×10^{-8}
Ex. 2	1.1×10^{-6}	4.2×10^{-7}	2.0×10^{-8}
Ex. 3	1.2×10^{-6}	2.0×10^{-7}	2.0×10^{-8}
Ex. 4	2.5×10^{-7}	1.3×10^{-7}	1.6×10^{-9}
Ex. 5	1.2×10^{-7}	1.8×10^{-7}	3.0×10^{-8}
Ex. 8	1.3×10^{-6}	2.2×10^{-7}	1.4×10^{-8}
Ex. 12	1.7×10^{-8}	0.8×10^{-7}	0.5×10^{-7}
Ex. 13	2.3×10^{-8}	1.5×10^{-8}	2.8×10^{-8}
Ex. 16	1.4×10^{-5}	4.8×10^{-6}	0.7×10^{-8}
Ex. 18	N T	1.0×10^{-7}	N T
Ex. 19	N T	1.0×10^{-7}	2.3×10^{-7}
Ex. 20	N T	2.2×10^{-7}	$> 10^{-4}$
Ex. 21	N T	0.6×10^{-6}	0.5×10^{-6}
Ex. 22	N T	2.1×10^{-7}	0.6×10^{-6}
Ex. 23	N T	2.2×10^{-7}	$> 10^{-4}$
Ex. 24	N T	0.6×10^{-7}	1.3×10^{-9}
Ex. 25	N T	1.7×10^{-6}	$> 10^{-3}$
Ex. 26	N T	4.0×10^{-7}	2.2×10^{-4}
Ex. 32	N T	4.2×10^{-7} (*)	7.0×10^{-5}
Ex. 35	N T	1.3×10^{-8} (*)	$> 10^{-4}$
Ex. 36	N T	1.1×10^{-6} (*)	2.1×10^{-5}
Ex. 37	N T	0.6×10^{-7} (*)	0.8×10^{-5}
Ex. 38	N T	0.5×10^{-7} (*)	$> 10^{-4}$

Ex. 39	N T	1.1×10^{-6}(*)	$> 10^{-4}$
Ex. 40	N T	1.8×10^{-7}(*)	$> 10^{-4}$
Eptastigmine	0.5×10^{-7}	2.9×10^{-7}	4.0×10^{-8}
Physostigmine	1.5×10^{-7}	0.5×10^{-7}	0.7×10^{-7}
Tacrine	N T	4.0×10^{-6}	N T

NT = not tested

(*) = incubation time 120'

The concentration inducing a 50% inhibition is indicated by the IC_{50}. The results reported in the Table 1 show that the products of the invention have a high acetylcholinesterase inhibitory activity.

Particularly active turn out the compounds of the Examples 1, 4, 5, 12, 13, 18, 19, 24, 35, 37, 38 and 40 whose potency is equal or even superior to that of eptastigmine or of physostigmine which turns out in turn superior to that of tacrine. The compounds of the Examples 20, 23, 25, 26, 35, 37, 38, 39 and 40 also show a potent and selective AChE inhibitory activity while have poor activity on the BuChE.

The compound of the Examples 1, 2, 25, 35, 38 and 40 has been estimated in comparison to eptastigmine and physostigmine for the acute toxicity (single administration) in mouse and rat.

The results are reported in Table 2.

TABLE 2

Toxicity tests (LD_{50})

	Mouse		Rat	
	os	iv	os	iv
Ex. 1	67	15	33	NT
Ex. 2	>50	NT	NT	NT
Ex. 25	NT	15	56	14
Ex. 35	NT	NT	40	3
Ex. 38	NT	NT	>40	NT
Ex. 40	NT	NT	>40	NT
Eptastigmine	25	7	23	5
Physostigmine	3.4	0.6	NT	NT

NT = not tested

LD_{50} is the dose (mg/kg) inducing 50% mortality.

The results show that the compounds of the series claimed in the present invention are provided with a low toxicity in the experimental animal.

Results of other experiments also show that the compound 1, administered to rats in doses of 0.5-1-2-4 mg/kg per os, is able to reduce the amnesic failure induced by scopolamine in the Passive Avoidance test.

The values of the dosages per os used in the Passive Avoidance test, if compared with the LD_{50} values, show that the claimed compounds have a high safety index.

Due to the above mentioned characteristics, the compounds of the present invention, comprising the compounds having formula (I) and their salts

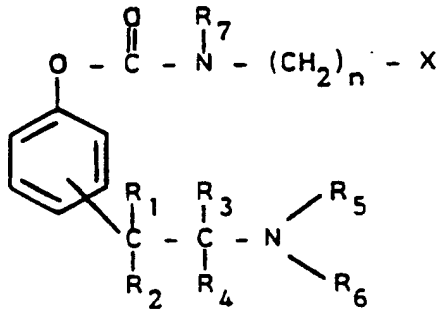
with pharmacologically acceptable acids, find a therapeutic application in every pathological form characterized by acetylcholine deficiency such as for example the diseases linked to memory deficit (Alzheimer Desease) or in the cerebral pathological forms of ischemic kind.

For such a purpose pharmaceutical compositions comprising effective quantities of said compounds mixed with pharmacologically acceptable diluents and excipients are prepared. Thus the invention refers also to the therapeutic method, to be applied in the human therapy in the pathologies characterized by acetylcholine deficiency, comprising oral or parenteral administration of a pharmacologically effective dose of said compounds.

The compound (I) dose to administer for the therapeutic treatment is comprised between 10 and 200 mg/die for the oral administration and between 2 and 20 mg/die for the parenteral administration.

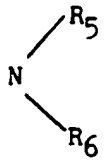
CLAIMS

1. Phenylcarbamate derivatives having the following general formula



wherein R_1, R_2, R_3 and R_4, equal or different, represent: hydrogen, linear or branched (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, arylalkyl, hydroxyl, or R_1 and R_2 together are $-(CH_2)_m-$ wherein m is an integer number from 2 to 5 and form a cycle from 3 to 6 carbon atoms;

R_5 and R_6, equal or different, represent: hydrogen, linear or branched (C_1-C_6) alkyl, arylalkyl, acyl or the group:

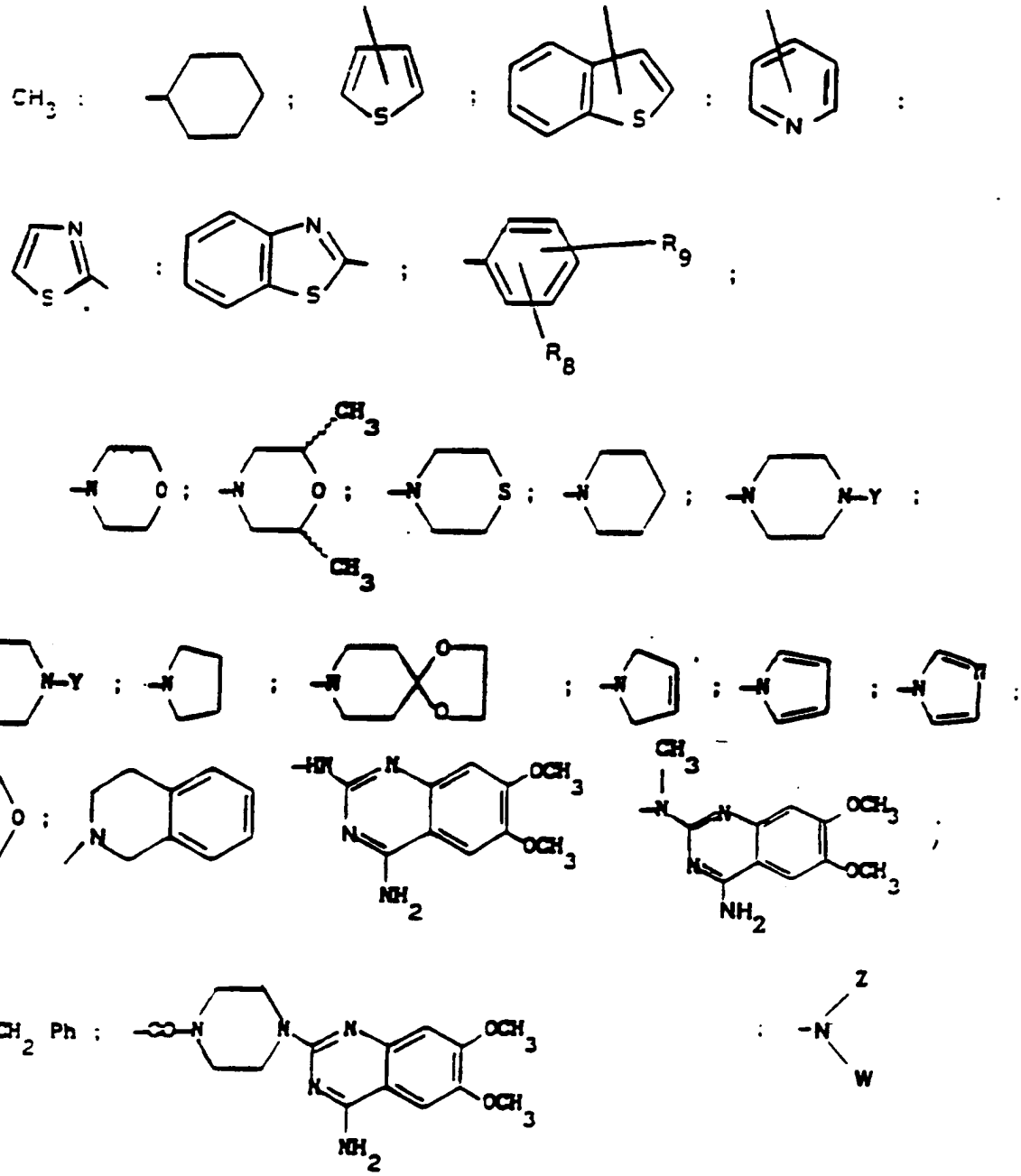


is a radical derivatived from the morpholine, piperidine, tetrahydroquinoline, tetrahydroisoquinoline, alkylpiperazine, arylpiperazine, arylalkylpiperazine, acylpiperazine, the dialkylaminoalkyl group being in para or meta position with respect to the carbamic group;

R_7 represents hydrogen or a linear or branched (C_1-C_4) alkyl;

n is an integer number from 0 to 20;

X is selected from the radicals

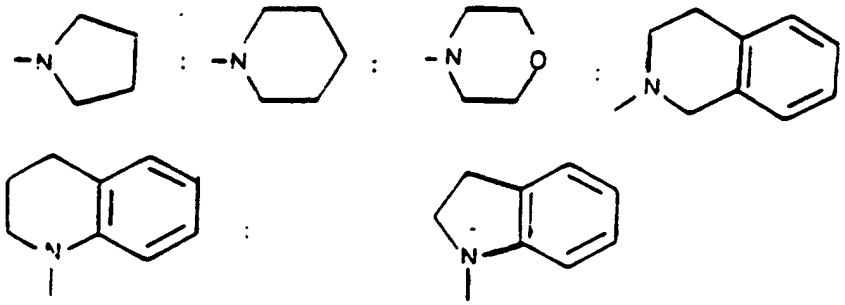


wherein R_8 and R_9, equal or different, represent: linear or branched (C_1-C_4) alkyl, halogen, methoxy, nitro, trifluoromethyl;

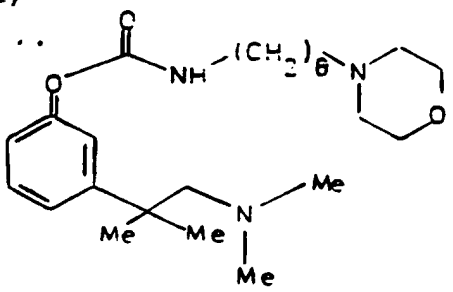
Y represents a linear or branched (C_1-C_4) alkyl, acyl, aryl, arylalkyl;

W and Z, equal or different, represent a linear or branched (C_1-C_4) alkyl, arylalkyl, methoxyethyl, methoxypropyl, methoxybenzyl;

or the $-N-(CH_2)_n-X$ group (R_7 on the N) is an heterocyclic group such as for example



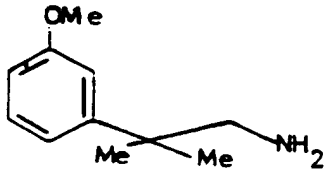
2. Process for the preparation of the phenylcarbamate derivative having formula (II)



(II)

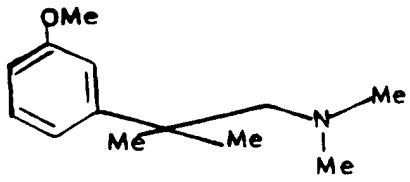
characterized by the fact that:

A) the compound having formula (III)



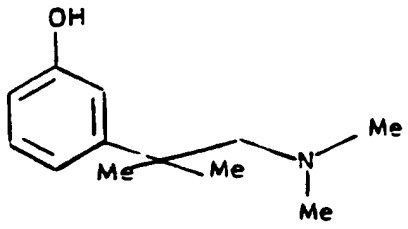
(III)

is made to react with formaldehyde in reductive amination conditions to obtain the compound (IV)



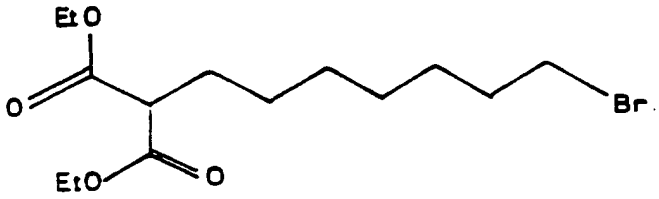
(IV)

B) The compound having formula (IV) is O-demethylated in acid conditions to obtain the compound having formula (V)



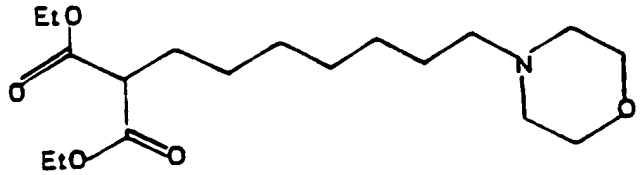
(V)

C) The compound having formula (VI)



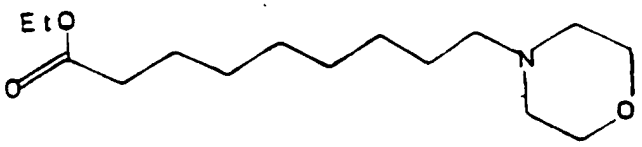
(VI)

is made to react with morpholine to obtain the compound (VII)



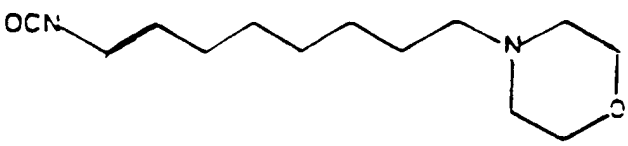
(VII)

D) The compound (VII) is monodecarboxylated to obtain the compound (VIII)



(VIII)

E) The compound (VIII) is submitted to hydrolysis, then transformed in acylazide and by Curtius rearrangement in isocyanate to obtain the compound (IX)



(IX)

F) The compound (V) dissolved in anhydrous toluene, is treated with metallic sodium and subsequently with the compound (IX) to obtain the desired compound (II).

3. Process as claimed in claim 2, characterized by the fact that said A) step is carried out treating in a polar or bipolar aprotic solvent the compound (III) with formaldehyde and with a reducing agent selected between sodium borohydride and sodium cyanoborohydride with molar ratio between (III) and formaldehyde of 1:10 and with molar ratio between said reducing agent and (III) of 4:1, at a temperature between 2 and 5 °C.

4. Process as claimed in claim 2, characterized by the fact that said B) step is carried out in an aqueous solution of HBr at 48% by weight at a temperature between the room temperature and 100 °C.

5. Process as claimed in claim 2, characterized by the fact that said B) step is carried out by treatment with a Lewis acid selected from aluminum chloride, boron fluoride and boron tribromide in an apolar solvent selected from benzene, toluene and chlorobenzene at a temperature between 25 and 80 °C.

6. Process as claimed in claim 2, characterized by the fact that said C) step is carried out in bipolar aprotic solvent selected from dimethyl formamide, dimethyl sulfoxide and acetone with a molar ratio between (VI) and morpholine between 1:2 and 1:3, at room temperature.

7. Process as claimed in claim 2, characterized by the fact that the D) step is carried out with a molar ratio between (VII) and boric acid between 1:1 and 1:2 at the acid melting point.

8. Process as claimed in claim 2, characterized by the fact that the E) step is accomplished by treatment with sodium hydroxide in boiling water, followed by the addition of acetone, of ethyl chloroformiate

dissolved in acetone and of tetrabutylammonium chloride at a temperature between -5 and 0 °C and by final treatment with sodium azide dissolved in water at 0 °C, the molar ratio between (VIII) and ethyl chloroformiate being comprised between 1:1 and 1:2 and the molar ratio between (VIII) and sodium azide being comprised between 1:2 and 1:3.

9. Process as claimed in claim 2, characterized by the fact that in the F) step said treatment of (V) with metallic sodium and with (IX) is carried out in an apolar solvent selected from benzene, xylene, chlorobenzene and toluene, at room temperature and with a molar ratio between (V) and Na comprised between 10:1 and 20:1 and between (V) and (IX) comprised between 1:1 and 1:2.

10. Pharmaceutical composition for the treatment of the pathological forms derived by acetylcholine deficiency containing an effective dose of a compound having formula (I) as claimed in claim 1 as an active substance or of one of its salts, together with pharmacologically acceptable diluents and excipients.

11. Composition as claimed in claim 10 in a form suitable to oral administration.

12. Composition as claimed in claim 10 in a form suitable to the parenteral administration.

13. Therapeutic method for the treatment of the pathological forms derived by acetylcholine deficiency comprising the administration of an effective dose of a compound having formula (I) as claimed in claim 1 or of one of its pharmacologically acceptable salts.

14. Method as claimed in claim 13, characterized by the fact that said administration is carried out per os in a dose between 10 and 200 mg/die.

15. Method as claimed in claim 13, characterized by the fact that said

administration is carried out parenterally in a dose between 2 and 20 mg/die.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/02752

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/13 C07C271/44 C07D239/95 C07C271/58 C07C271/56
A61K31/535 A61K31/27 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 110, no. 7, 13 February 1989, Columbus, Ohio, US; abstract no. 57493, TAMURA, TOSHIYA ET AL. page 673 ; see abstract see RN 118511-43-6, Carbamic acid, (3-chlorophenyl)-, 3-[2-(1-piperidinyl)ethyl]phenyl ester see RN 118511-44-7, Carbamic acid, (3-chlorophenyl)-, 4-[2-(1-piperidinyl)ethyl]phenyl ester & JP,A,63 170 356 (YAMANOUCHI PHARMACEUTICAL CO.) --- -/--	1,10,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1995	21. 11. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Seufert, G

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INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/02752

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, 1947, LETCHWORTH GB pages 191 - 195 R. E. DAVIES ET AL. 'Investigations on the influence of chemical constitution upon toxicity. part III. Compounds related to miotine' see page 191, compound II; table I, compounds (b)4, (c)4, (c)5; see page 191, last paragraph - page 192, line 8; page 192, line 21 - line 25	1,10
A	see page 196, line 4 - line 10	2
X	'CA Registry Handbook, 1977' , AMERICAN CHEMICAL SOCIETY see RN 63982-43-4, 63884-71-9	1
A	EP,A,0 193 926 (YISSUM RESEARCH AND DEVELOPMENT COMPANY) 10 September 1986 cited in the application see claims; examples; tables 1-3	1,10
A	EP,A,0 154 864 (CONSIGLIO NATIONALE DELLE RICERCHE) 18 September 1985 cited in the application see claims; examples	1,10
A	EP,A,0 575 954 (MEDIOLANUM FARMACEUTICI) 29 December 1993 see claims; examples	1,10
A	WO,A,92 00072 (HAMER ET AL.) 9 January 1992 see claims	1,10

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/02752

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK : ALTHOUGH CLAIMS 13-15 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS THE COMPOUNDS.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/EP 95/02752

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP-A-63170356	14-07-88	NONE		
EP-A-0193926	10-09-86	AU-B-	595504	05-04-90
		AU-B-	5428486	11-09-86
		CA-A-	1284501	28-05-91
		JP-C-	1629293	20-12-91
		JP-B-	2055416	27-11-90
		JP-A-	61225158	06-10-86
		US-A-	4948807	14-08-90
EP-A-0154864	18-09-85	EP-A-	0354594	14-02-90
		JP-C-	1690155	27-08-92
		JP-B-	3054952	21-08-91
		JP-A-	60208982	21-10-85
		US-A-	5306825	26-04-94
		US-A-	4831155	16-05-89
EP-A-0575954	29-12-93	CA-A-	2099648	26-12-93
		JP-A-	6206882	26-07-94
		US-A-	5302593	12-04-94
		US-A-	5424451	13-06-95
WO-A-9200072	09-01-92	AU-B-	649953	09-06-94
		EP-A-	0538248	28-04-93